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10/791,209	03/01/2004	Soonkap Hahn	81671	3988

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EXAMINER	
SKOWRONEK, KARLHEINZ R	
ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/791,209	HAHN, SOONKAP	
	Examiner	Art Unit	
	Karlheinz R. Skowronek	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-16 and 22-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *14* is/are allowed.

6)☒ Claim(s) *1-3, 5-16 and 22, 24-25* is/are rejected.

7)☒ Claim(s) *2 and 23* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 1-3, 5-16, and 22-25 are pending.

Claims 4 and 17-21 are cancelled.

Claims 1-3, 5-16, and 22-25 are being examined.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 and 5-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "said CGG repeat probes" in step h, line 4. There is insufficient antecedent basis for this limitation in the claim. Claims 2, 3, and 5-13 are also rejected because it depends from claim 1, and thus contain the above issues due to said dependence.

Claim 1 is unclear with regards to step e what is being bound to the solid phase. Both strands of DNA produced in the PCR reaction will have single stranded segments that will be bound in step e. Therefore, step e is not clear regarding the outcome of the step.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This rejection is reiterated from the previous office action

Claims 1, 3, 5-12, 15-16, 22, 24, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (Korean IPO Pub. No. 10-2000-0072201 Pub Date 17 August 2000), in view of Beattie et al. (US PAT 6,268,147) in view of O'Connell et al. (Clinical genetics, Vol. 61, p. 13-20, 2002) and in view of Smith et al (US PAT 5,753,439).

The claims are drawn to a method of detecting mutations that are indicative of Fragile X syndrome by testing obtained genomic DNA using labeled oligonucleotides to determine the number of CGG repeats in the obtained genomic DNA.

Kim teach a method of diagnosing Fragile-X syndrome by using DNA Probes to identify the number of CGG repeats in the obtained genomic DNA. Specifically, Kim teaches obtaining a genomic DNA sample (para. 16). Kim teaches the generation of single stranded DNA (para. 18, line 6). Kim teaches the hybridization of two differentially labeled probes to targets within the denatured each probe directed to a different genomic region of FMR1 gene; one probe being targeted to Short Tandem Repeats (STR) or Short Tandem Repeat Polymorphisms (STRP) CGG or GCC and one probe

being targeted to a region of FMR1 gene (para. 48, line 6). Kim shows the immobilization of the labeled target to a solid support (para.18, line 6), separating the hybridized DNA from non-hybridized nucleic acids. Kim teaches measuring the colorimetric intensities of the CY3 and CY5 fluorescent dyes that label the different probes and determining a ratio between cy3 and cy5 then compared to a known control to determine the number of CGG or GCC STR repeats (para. 49). Kim shows that the target oligonucleotides for the CGG repeats contain 3-10 repeats and specifically show target oligonucleotides for the CGG repeats having 6 triplets (para 49).

Although Kim does not employ PCR directly in the method of identifying the number of STR's in FMR1, Kim shows that the application of PCR to amplify DNA fragments of the region of the FMR1 gene surrounding the CGG STRs can also employed in the analysis of Fragile-X syndrome. The primers of Kim can be used to amplify the same region of FMR1 as the primers of the instant invention. SEQ ID NO:1 of the instant application is targeted to the 5' untranslated region of the FMR1 on the X chromosome. The primer of Kim on paragraph 48, line 6 is directed a similar region of the X chromosome in the 5' untranslated region of FMR and is labeled with biotin. SEQ ID NO: 2 is within the FMR1 gene, 3' to the repeat region. Similarly, Kim shows a primer on paragraph 48, line 5, which targets bases 250-221. The primers of Kim are suitable for PCR amplify the repeat region of the FMR1 5'-untranslated region. Kim suggests that a method better than electrophoresis and southern blotting is needed to quickly and efficiently analyze the DNA of the 5' untranslated region FMR1 gene.

Kim does not show the use of microarray technology to capture the differentially labeled hybridized target STR's; does not show amplification of DNA by PCR and does not show the use of an exonuclease to generate single stranded DNA.

O'Connell et al. shows the detection of fragile X through a quantitative measurement program for trinucleotide repeats. O'Connell et al. shows the use of PCR to amplify the 5'-untranslated region of FMR1 using oligonucleotides directed to a contiguous region of the FMR1 gene and to a region of the X-chromosome 5' to the repeat region (p.14, col 1). The primers of O'Connell et al. overlap the primers of SEQ ID NO: 1 and 2. O'Connell shows the primers are used to amplify the 5'-untranslated region of FMR1 containing CGG repeats. O'Connell et al. shows that fragile X testing is usually conducted using PCR. O'Connell et al. shows a method of an optimized PCR amplification method to correctly measure the number of CGG repeats in genomic DNA (p. 14 col. 2 to p. 15 col. 1). It is desirable to correctly measure the number of repeats in the 5'untranslated region of the FMR1 gene because the number of CGG repeats is directly linked to the fragile X phenotype and it's diagnosis. O'Connell et al. shows that accurate (CGG)n size determinations are essential to accurate diagnosis of fragile X (p.14, col. 1).

Beattie et al. show a method of analyzing STRP's by microarray. Beattie et al. shows the use of exonucleases to generate single stranded DNA (col. 29, line 34-43). Beattie et al. shows the advantage to generating single stranded DNA is that re-annealing of complementary target strands can be avoided (col. 29, line 30-32). This is advantageous because the complementary strands may compete with the hybridization

of the target strands to the arrayed capture probes (col. 29, line 32-33). Beattie et al. teach the use of microarray technology to capture nucleic acids (abstract and col. 37-38). Beattie et al. shows that the array has a plurality of spots in which probes to the contiguous segment are linked to a solid support (col. 37).

Smith et al. shows a method of nucleic acid analysis for rapidly determining the length and sequence of a target. Smith et al. shows an array can be constructed to separately target a contiguous sequence and the repeat regions (col. 8, line 41-43). Smith et al. shows that hybridization can be used to rapidly and accurately detect and identify numbers of repeated sequences (col 4, line 3-6).

It would have been obvious to one of skill in the art to modify the method of Kim differentially targeting the CGG repeats and a 3'- contiguous region using different colorimetric probes with the method of amplifying the 5'-untranslated region of FMR1 containing CGG repeats of O'Connell and the method of producing single stranded DNA using exonuclease of Beattie and the plurality of targeting probes of Smith et al, because O'Connell et al. shows that accurate CGG size determinations are essential to accurate diagnosis of fragile X. It would have been further obvious to modify Kim with O'Connell et al., Beattie et al., and Smith et al. because Beattie et al. shows the advantage to generating single stranded DNA is that re-annealing of complementary target strands can be avoided because the complementary strands may compete with the hybridization of the target strands to the arrayed capture probes. It would have been further obvious to modify Kim with O'Connell et al., Beattie et al., and Smith et al.

because Smith et al. shows that hybridization can be used to rapidly and accurately detect and identify numbers of repeated sequences.

Response to arguments

Applicant's arguments filed 13 July 2007 have been fully considered but they are not persuasive. Applicant argues that the limitations of claim 4 have been incorporated into claim 1 distinguishing it over the prior art. This is not persuasive. Upon further consideration, the amendment of claim 1 is obvious over Kim in view of O'Connell et al., in view of Beattie et al., and Smith et al. Kim describes the hybridization of colorimetric-labeled oligonucleotides which separately target for CGG and contiguous nucleic acid segments.

Applicant argues that the references cannot be combined. The argument is not found persuasive. First, each reference applied is directed to solving the same problem, namely the enumeration of STRPs in DNA. Second, the methods of the references are complementary. Kim shows two primer sequences that are similar to the primer sequences used in O'Connell to amplify the 5'-untranslated region of the FMR1 gene for analysis of the short tandem repeat CGG. Seeing this, one of ordinary skill would have used the primer sequences of Kim to amplify the same region of FMR 1 as in O'Connell with a reasonable expectation of success demonstrated by O'Connell. Kim also shows primers that have a biotin tag incorporated and are used to capture the labeled oligonucleotide hybridized DNA. Beattie et al. show that single stranded target DNA can be prepared with PCR amplified, biotin labeled DNA. Complementary to the method of Beattie et al, Kim shows biotin labeled primers suitable for use in the methods of Beattie

et al. Beattie et al shows in example 1 that PCR with biotin labeled primers can be used to generate single stranded DNA. As an alternative, Beattie et al. also shows that single stranded DNA can generated using an exonuclease, without the use of biotin. Beattie et al. shows that the application of arrays to analyze DNA is equally applicable to bead technology (col. 30, example 18).

Kim also shows that number of CGG repeats can be enumerated by analyzing the ratio of CY3 fluorescence (probe directed to the contiguous region) to CY5 fluorescence (probes directed to the CGG repeat region). Beattie et al. shows that short tandem repeats can be analyzed by microarray. Smith et al. shows that the analysis of short tandem repeats can be accurately sized using a plurality of probes directed to constant contiguous region and probes with increasing numbers of repeat sequences. The references are combinable because they are all directed to obtaining the same result, namely the enumeration of tandem repeats in DNA sequences.

Applicant argues that Kim teaches away from the use of PCR to analyze the repeat region of FMR1. This is not persuasive. Applicant has misinterpreted Kim. Kim shows that because the high GC content of the repeat region, the direct analysis of the repeat region by electrophoresis is difficult to analyze. It is well known that PCR only amplifies DNA and must be combined with another technique to visualize the amplified products. For example, in O'Connell et al. 2 primers are used to amplify the same region of the FMR1 gene as Kim and the instant application and using electrophoresis to visualize and analyze the amplified repeat region of FMR1. Thus Kim teaches away

from using electrophoresis and southern blotting for the analysis of the repeat region of FMR1, but not the use of PCR.

Allowable Subject Matter

Claim 14 is allowable. After a diligent search or the art, it is found that the prior art does not fairly teach the formula, N=30+(A-1.03)66.4, used to calculate the number of CGG repeats in FRAXA/5' untranslated FMR1 region.

Claims 2 and 23 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The equation used to calculate the number of repeats is the point of novelty of the presently claim invention.

Upon reconsideration, the objection of claims 4, 13, 16, and 24 is withdrawn.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karlheinz R. Skowronek whose telephone number is (571) 272-9047. The examiner can normally be reached on Mon-Fri 8:00am-5:00pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie A. Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

14 October 2007

/KRS/
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15 October 2007
JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER